ABOUT THE ATHENA TRIAL

Study Summary

• We are inviting **adults aged 50 years or older with a diagnosis of shingles** to take part in the ATHENA research study.

• The study aims to find out whether taking **a low dose of amitriptyline soon after getting shingles** can prevent pain associated with shingles.

• If you take part, you will be prescribed **either amitriptyline or a placebo ("dummy") tablets**.

• Neither you nor your doctors will **be able to choose or know which tablets you get**. Participants will be asked to take the study medication for **70 days**.

• As normal, you may also be prescribed an **antiviral medication to treat the shingles**.

• You will be asked to **complete questionnaires** at the start and then six times over 12 months, to find out how you get on.

• By taking part in this study, you will help us find out **whether amitriptyline should be prescribed to adults diagnosed with shingles, to prevent long-term pain.**

• If you decide to take part in the study, you can leave at any time without giving a reason.

How to take part

• Before you decide to take part, **please take time to read this information sheet**. It is important that you understand what the study is about, why it is being done, and what it would involve for you.

• **Please ask** if there are any parts of this information sheet that you do not understand or if you would like further information.

Contact details

Email: athena-study@bristol.ac.uk

Website: www.bristol.ac.uk/athena-study

Telephone: 0117 331 4532

Twitter: @AthenaStudy

Postal address: ATHENA Study,

Centre for Academic Primary Care,

Bristol Medical School, 39 Whatley Road, Bristol BS8 2PS

Thank you

Thank you for taking the time to read this information sheet and for considering your participation in the ATHENA Study.

What is the purpose of the study?

The aim of the ATHENA study is to find out whether a medicine called amitriptyline stops adults with shingles getting "post-herpetic neuralgia" (nerve pain after shingles).

We are also interested in understanding how common it is for people to have problems with the treatment and how people find taking the medication alongside any other tablets.

We are also interested to compare the cost and effectiveness of amitriptyline with other pain-relieving treatment and the use of healthcare resources.

Why is the study being done?

Herpes zoster or "**shingles"** causes a painful, blistering rash, which normally goes away after four weeks:

• Approximately 30% of people get shingles.

• It is more common in people over the age of 50.

The most common complication of shingles is **post-herpetic neuralgia**, an unpleasant "nerve pain" that persists after the rash has gone:

• This pain can reduce the quality of life of those affected and can be difficult to treat with standard painkilling medication.

Amitriptyline is a medicine first used many years ago to treat depression:

• Nowadays it is more commonly used to treat pain.

• We do not know whether it can also prevent the nerve pain of post-herpetic neuralgia.

A previous small study suggested that a low dose of amitriptyline taken when the shingles rash first appears can prevent post-herpetic neuralgia for some patients. This needs to be proven in a bigger trial before the medication can be routinely prescribed for this purpose.

Rather than acting as an antidepressant, we think amitriptyline may work on nerve growth factor receptors in the body to prevent nerve damage

We need the help of 846 people with newly diagnosed shingles to join the study to enable us to answer the question, **"Does taking amitriptyline when the rash of shingles first appears prevent post-herpetic neuralgia?"**

This study has been designed by expert researchers and doctors, with the help of patients who have experienced shingles and post-herpetic neuralgia.

Why have I been invited to take part?

You have been invited to take part in this study because you have been diagnosed with shingles.

To be eligible to take part you need to:

• Be 50 years old or older.

• Be diagnosed with shingles by your GP soon after getting the shingles rash.

• Have a healthy immune system and be able to take amitriptyline.

• Be able to complete online or paper questionnaires about your symptoms and use of healthcare.

• Be able to provide informed consent to take part.

What is involved if I take part?

You will be sent the study medication, either **amitriptyline or placebo** ("dummy") tablets. You will not be able to tell by looking at them which tablets you have. You will be asked to take these **daily for 10 weeks**.

Even if you think you are taking the placebo, you are a very important part of the study. Giving some people a dummy tablet is the only way we can really tell whether the medication makes any difference.

To find out how you get on, we will **telephone you** around 1 week and 3 weeks after you start taking your tablets. We will ask all participants to **answer questionnaires** at the beginning and then 30, 60, 90, 120, 180 and 360 days after your shingles rash started.

• The questionnaires will ask about shingles-related pain, your quality of life, well-being, medication use and any side effects.

• You will be offered three gift vouchers of £10 (at the start, after 3 months and after the final questionnaires) to thank you for your time spent completing these questionnaires.

Optional extras. If you agree, we may also:

• Audio-record conversations where the ATHENA study is discussed with you. This is to see how the study is explained to you and how we can improve this. You will be asked for our verbal permission, before anything is recorded.

• Invite you to talk with a researcher. There are two different types of interviews you may be invited to take part in. The first type is a short 5-20 minute interview to get your views and experiences of being invited to take part in the study. The second type of interview focuses on your experience of taking part in the study and the study medication. This is more detailed and may take up to an hour. It would be done by phone, video call or in person. With your permission it would be recorded. You will be able to speak to a researcher to discuss this further before agreeing to take part.

If you do not want to do either of these things, you can still take part in the main study.

Deciding whether to take part

Please remember:

• **Participation is voluntary**, it is your choice whether you take part in this study, or not. Your usual care will not be affected either way.

• **If do not understand anything** or have any questions, **please ask**.

• If you do decide to take part, **you are free to leave the study at any time,** without giving a reason.

What happens if I would like to go ahead?

A member of the study team will contact you to answer any questions you may have, and ensure you understand what you are signing-up for.

If you agree, you will:

• Complete a **consent form** confirming that you understand the study and are willing to take part.

• Complete a **baseline questionnaire** so that we know how things are for you at the start, to compare with.

• Be allocated to receive either amitriptyline or placebo (“dummy”) tablets. (There is more detail next on how this means.)

How is the treatment allocated?

A member of the study team will contact you to answer any questions you may have, and ensure you understand what you are signing-up for.

If you agree, you will:

• Complete a **consent form** confirming that you understand the study and are willing to take part.

• Complete a **baseline questionnaire** so that we know how things are for you at the start, to compare with.

• Be allocated to receive either amitriptyline or placebo ("dummy") tablets. (There is more detail next on how this means.)

Neither you, your doctor nor the research team will know which tablet you have been allocated.

• This is important so that perceptions about the medication do not affect the results of the study.

• However, your safety comes first, and if there is a medical reason, this information will be available 24/7 via an emergency helpline.

Receiving the study medication

Receiving your medication. The medication will be posted to you or if preferred, we may be able to send it to your GP surgery.

Taking the medication. You will be given instructions on how to take the study medication. You will start by taking one tablet every day, increasing over two weeks to three tablets every day.

How do we decide which dose of medication you should take? A member of the research team will arrange to speak with you twice, around one week and three weeks after starting the medication to see how you are getting on:

• The researcher will ask you how many tablets you are taking, whether the medication is suiting you and answer any questions you may have about the study.

• If you experience troublesome side effects, we may advise you stay on the current dose, or go down to a lower dose.

Once you have decided the dose most suitable for you, you will be asked to continue taking this for a total of 10 weeks.

What is the medication being tested?

The medication being tested is called amitriptyline.

• It was originally used at high doses (75mg to 150mg) for the treatment of depression.

• Nowadays, it is more commonly used at low doses (10mg to 30mg) for nerve pain and other problems.

Because amitriptyline has been used by patients for a long time, we already know a lot about its safety, effectiveness, and side effects in other conditions.

Does the medication have any side effects?

Like all tablets, even at low dose some people may get side effects with amitriptyline.

• One important aim of this study is to understand how commonly people have problems with amitriptyline. (It is possible that the side effects experienced by adults with shingles may be different from the population treated for other types of pain.)

• We will therefore be asking you about possible side effects in the questionnaires that we send you.

Between 1 in 4 and 1 in 15 people may experience side effects from amitriptyline, the most common being:

• *constipation* • *dizziness* • *dry mouth*

• *drowsiness* • *sedation* • *nasal congestion*

• *weight gain* • *excessive sweating*

• *blurred vision*

Minor side effects commonly disappear as your body gets used to the medicine.

Some people are at higher risk of developing side effects from amitriptyline, for example if you have certain other medical problems, are frail or

are taking other particular tablets. Your GP will confirm that it is safe for you to take part.

If you want more detail about the possible side effects of amitriptyline, they can be found in the Summary of Product Characteristics (SmPC) leaflet available on the ATHENA website (www.bristol.ac.uk/athena-study). You can also talk to the research team if you have any queries or concerns.

What will happen if I get side effects?

Depending on how troublesome the side effect is, you may:

- Continue with the medication and see if the symptoms resolve
- Take a lower dose.
- Discuss it with your GP.
- Seek treatment for the side effect.
- Stop the medication completely.

You can carry on taking part in the study even if you have to stop the tablets because of side effects. **Your responses to the questionnaires will still be valuable.**

Will it affect other medications I take?

You will only be asked to join the study if you are not taking medications that the study medication may interfere with.

You can continue taking all your other medications as normal throughout the study. Your GP can prescribe most other medications normally. However, you cannot be prescribed amitriptyline at the same time. We will let your doctor know that you are taking part in this study so they can consider this when prescribing any other medication to you.

If you see any new doctors or take any new medication, it would be important to let the health care professional know that you are taking part in this study.

As is usual care in shingles, everyone will be offered an antiviral treatment by their GP, usually for seven days.

You are also able to continue to have any vaccination that you require during your time in the study (including the shingles vaccine).

There is no known relationship between amitriptyline and Covid-19 vaccinations. Therefore, having a Covid-19 vaccine before, during or after your time in the study, should not matter.

What will happen when the study treatment stops?

At the end of the study treatment period, you can just stop taking the tablets, but we will ask you to continue to answer the study questionnaires until 12 months from when you were first enrolled.

At the end of the whole study, you will have the option of finding out which tablet you were taking.

If you and your GP want, you can still take amitriptyline after finishing your study treatment period.

What are the alternative treatments?

Other treatments are available to <u>treat</u> shingles-related pain but as far as we know, none can <u>prevent</u> pain (post-herpetic neuralgia), which is why we are doing this study. You can still have all other usual care from your GP/hospital.

What are the possible benefits and downsides of taking part?

Possible benefits from taking part are:

- The study medication may prevent you from getting the post-herpetic neuralgia, but there is no guarantee.

• Some people find taking part in research rewarding and benefit from the extra contact from being part of the study.

• Even if you do not directly benefit from taking part in this study, your involvement will inform future treatment recommendations for adults who experience shingles.

Possible downsides from taking part are:

• Getting side effects from the study medication.

• Not being able to take non-study amitriptyline or other specific tablets because you may be taking amitriptyline as part of the study.

Participating in this study does not replace other services for any physical or mental health problems that you may be receiving, and you should continue to seek support from your GP and any other services as you would usually do.

If I take part, can I change my mind and leave the study?

Yes. If you decide to take part, **you are free to leave the study (withdraw) at any time**. You can do this by telling the study team (our contact details are on the last page of this leaflet).

If you decided to stop the medication, you can still remain in the study. It is very important that we try and get results from everyone who takes part in the study, whether they continue with the medication or not. **By continuing to complete the questionnaires, you will still be helping.**

If you want, you can withdraw from the study completely, including not completing any more questionnaires. You would not have to give a reason for withdrawing, and your medical care and legal rights would not be affected. If this happened:

• We would use any information we have already collected about you to use in our analysis of the study results.

• If you gave permission, we would still collect information about your health from central NHS records/your hospital/your GP, for the time you were due to be taking part in the study.

• We may ask if you would be willing to discuss your reasons for leaving the study with a researcher.

What if new information becomes available during the study?

Sometimes we get new information about the condition or medication being studied. If this happens, the study team will tell you and discuss whether you should continue in the study. If you decided not to continue, you would be withdrawn from the study. If you did continue in the study, you may be asked to sign an updated consent form.

How long does the study last and what will happen to the results?

The study is expected to run from 2021 through to 2024.

• Once completed, the overall results will be published in medical journals and presented at conferences attended by healthcare professionals and researchers.

• The results will also be shared with the wider public using accessible summaries through our website and social media.

• We will also send you, if you wish, a newsletter with the results of the study, which are expected in 2024.

No one will be able to identify you from any of the study reports/publications.

Who funded this study, who is the sponsor, and who is managing this study?

The study is being funded by the "research arm" of the NHS, the National Institute for Health Research Health Technology Assessment programme (NIHR HTA reference 129720). This

study is not funded nor is there any involvement by any pharmaceutical company.

The research is led by a team of experienced doctors and researchers and is overseen (sponsored) by the University of Bristol.

The Bristol Trials Centre is responsible for running the study.

Will my data be used in future research?

Other researchers may request to access **anonymised data** (i.e. data that you cannot be identified from) from this study in the future, for example to combine the results of our study with others similar studies. These researchers may be outside of the UK, EU and EEA.

If you take part in this study, **anonymised data** collected in this study may be used in future ethically approved studies; this will never include names or contact details, and it will not be possible to identify individual participants.

For more detailed information about how we will process, store and share any information that you give us, please see the blue pages at the back of this leaflet.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee (REC) to protect your safety, rights, wellbeing, and dignity.

This study has been reviewed and approved by South West - Central Bristol Research Ethics Committee 21/SW/0130, the Health Research Authority and the Medicines and Healthcare products Regulatory Authority (MHRA).

Additionally, during the duration of the study, independent Data Monitoring and Trial Steering Committees will monitor the study to ensure it is conducted according to good research practice.

What if there is a problem?

If you have a concern regarding your care as a patient, please discuss this with your GP or specialist.

We do not expect taking part to affect any private medical insurance, but if relevant, please check with your insurers before agreeing to take part in the study.

If something goes wrong and you are harmed during the study and this is due to someone's negligence then you may have grounds for legal action, but you may have to pay your legal costs. The normal National Health Service (NHS) complaints mechanisms will still be available to you.

What if I have a concern or complaint?

If you have any questions (or concerns) about any aspect of this study, or your treatment or health whilst on the study, please speak to a member of the research team using the details on the back page.

If you remain unhappy with any aspect of the study, please email the sponsor (research-governance@bristol.ac.uk).

If you are still concerned and wish to complain formally about your healthcare or any aspects of this study, you can do this through the NHS Complaints Procedure, either by post, telephone, or email.

Post: NHS England, PO Box 16738, Redditch, B97 9PT. **Telephone:** 0300 311 22 33. **Email:** england.contactus@nhs.net *(Please state: 'For the attention of the complaints team' in the subject line).*

You can visit their website for further information: **https://www.england.nhs.uk/contact-us/complaint /complaining-to-nhse/**

ABOUT MY DATA

If you are interested, these pages tell you more about how we process, store and share any information that you give us.

How will the information I provide be kept confidential?

We are committed to handling the information (data) used in the ATHENA study securely and confidentially. Your data will be stored and used in compliance with the relevant, current data protection laws; Data Protection Act 2018 and General Data Protection Regulation 2018 (GDPR).

We will use information from you and/or your medical records to undertake this study and the University of Bristol will act as the data controller.

• This means that we are responsible for looking after your information and using it properly.

• Personal information such as your name, date of birth, email address, and phone number will be stored on a secure database managed by the central research team (at the University of Bristol).

The University of Bristol will securely keep identifiable information about you for at least five years after the study has finished; this is considered good practice for clinical trials.

It is a requirement that your records in this research, together with any relevant medical records, can be looked at by authorised staff working for the Sponsor or the Regulatory Authorities. Their job is to check that research is properly conducted and the interests of those taking part are adequately protected.

With your permission, we may tell your doctor/GP if we have concerns about your health or well-being. However, if there is a risk of harm to you or others, we may share such information with your doctor without your consent.

How will we use information about you?

We will need to use information from you and/or from your medical records for this research project.

• People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

• We will keep all information about you safe and secure.

• Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

• We need to manage your records in specific ways for the research to be reliable. This means that we will not be able to let you see or change the data we hold about you.

• You will have the option on the consent form to potentially take part in future research using your anonymised data saved from this study.

If you consent to recording of discussions with study staff and/or interviews, then the recordings will be securely transferred and transcribed in part or full by University of Bristol employees or their authorised representatives.

• Transcripts will be anonymised so that you cannot be identified from them.

• Audio recordings will be transcribed by an employee of the University of Bristol or an approved transcription company. Data will be transferred by means of secure filestores and transcribers will be bound by a confidentiality agreement.

• The University of Bristol will securely retain audio-recorded data and may use anonymised quotations and parts of voice modified audio-recordings for training, teaching, research, and publication purposes for this and future studies, but we will ensure that you cannot be identified.

• With your permission, anonymised transcripts of audio-recordings may be made available by controlled access to other researchers outside of the ATHENA study who secure the necessary approvals. Again, we will ensure you cannot be identified.

• Data from the anonymised transcripts may be used for purposes not related to this study, but it will not be possible to identify you from them.

If you agree to take part in the ATHENA study, once you have completed the 12 months, we would **collect information from your GP** about your health for the time you were taking part in the study. This would not take up any of your time and would be done directly and securely with the GP practice.

We may also collect some data about you/your healthcare from **information resources such as NHS Central Registers or other registries including those managed by NHS Digital** (formerly Health and Social Care Information Centre (HSCIC)), Information Services Division Scotland (ISD), Patient Episode Database for Wales (PEDW), or Office for National Statistics (ONS). These public bodies routinely collect information from hospitals on behalf of the Government.

• To access this information, we will securely share some identifiable information with the relevant registry (e.g. full name, gender, NHS number, postcode, date of birth, and study number).

• If the requested information is available, the registry will return it securely to the University of Bristol where it will be analysed by the University of Bristol study team working on the study.

Who will you share information about me with?

Renaclinical are the company who will be providing you with the medication from their pharmacy. They will be given your personal information so they can send you the correct medication (amitriptyline or placebo). **In an emergency, they will be the organisation who will be able to identify which medication group you are in.** The information provided to them will be kept securely; they must follow our rules about keeping your information safe.

"Sealed Envelope™" are the company who provide the randomisation software which helps to enable the process of treatment allocation. We will provide "Sealed Envelope" with relevant information about you to enable their system to allocate which medication you will receive. The information provided to them will be kept securely and they will not be given patient names or contact details.

OneCare is an "umbrella" organisation based in Bristol that supports GPs in their use of electronic medical records, EMIS Web. Onecare will be helping us retrieve the relevant partially-anonymised data from your GP medical records, if you give consent for us to do so.

University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) carry out monitoring and safety reporting for the University of Bristol. To carry out these activities, UHBW may need to have access to your medical records where it is relevant to you taking part in the research.

If you sign up to receive the study newsletter, which will give regular updates on the progress of the study and news relating to the research, your email address will be stored by an **online newsletter provider** (such as "MailChimp®" or other similar provider), but cannot be used by them for any other purpose.

• You will be able to unsubscribe from the mailing list at any point, if you wish.

More information about how your information is used

You can find out more about how we use your information at:
www.hra.nhs.uk/information-about-patients
www.bristol.ac.uk/secretary/data-protection/policy/research-participant-fair-processing-notice or by asking the research team, see the front page for contact details.